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[3+2] CYCLOADDITION OF SELENO- AND THIOALDEHYDES WITH CYCLIC AZOMETHINE IMINES

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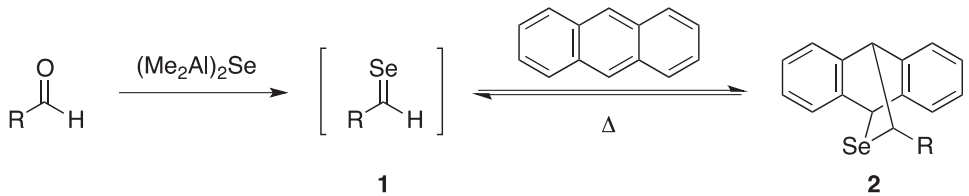
Abstract – Reaction of seleno- and thioaldehydes with cyclic azomethine imines in refluxing toluene gave [3+2] cycloadducts as a diastereomeric pure form in high yields. Thermal cycloreversion of the [3+2] cycloadducts regioselectively occurred to regenerate seleno- and thioaldehydes which can be trapped in situ by 2,3-dimethyl-1,3-butadiene.

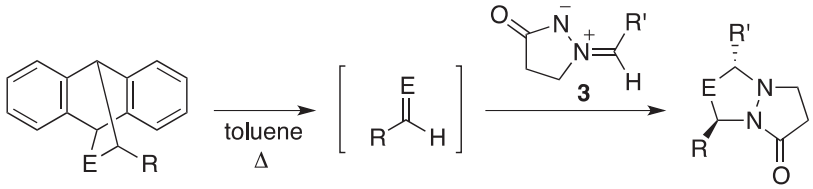
Selenocarbonyl compounds, for example, selenoketones, selenoaldehydes, and selenoamides, often exhibit unique reactivities that can not be seen in chemistry of the corresponding carbonyl compounds. Especially, cycloaddition reactions involving selenocarbonyl compounds have attracted much attention due to their high synthetic potential for construction of selenium-containing heterocyclic compounds.[1-6] As for the synthetic route of the selenocarbonyl compounds, we have developed a convenient direct conversion of carbonyl compounds to the corresponding selenocarbonyl compounds by reaction with bis(dimethylaluminum) selenide in high yields.[7-20] Among several selenocarbonyl compounds, selenoaldehydes (**1**) can be hardly isolated in general because they are extremely unstable compounds in air, but they can be trapped by anthracene in situ to give [4+2] cycloadducts **2** as stable and isolable



Scheme 1. Generation and Trapping of Selenoaldehydes

compounds.[16-19] We have also developed that thermal retro hetero-Diels Alder reaction of **2** at approximately 110 °C restores **1** under neutral conditions, and that they react with linear 1,3-dipole molecules such as nitrile oxides and nitrile imines to give selenium-containing five-membered ring products, 1,4,2-oxaselenazoles and 1,3,4-selenadiazoles, respectively.[21] Our continuing interest on the synthesis of selenium-containing heterocycles let us examine reactions employing some nonlinear 1,3-dipoles, but good results have not been obtained. In this study, we found that by using cyclic azomethine imines, which are representative rigid nonlinear 1,3-dipoles that often used to synthesis of diaza-heterocycles by reaction with various unsaturated compounds,[22-32] high-yield synthesis of novel selenium-containing bicyclic heterocycles could be achieved by reaction with selenoaldehydes **1** generated thermally in situ from **2**. Moreover, we also clarified that the reaction could be applied to synthesis of sulfur-containing analogues by the reaction using thioaldehydes.

Table 1. [3+2] Cycloaddition of Seleno- and Thioaldehydes with Cyclic Azomethine Imines[a)]



2 (E = Se)
6 (E = S)

1 (E = Se)
5 (E = S)

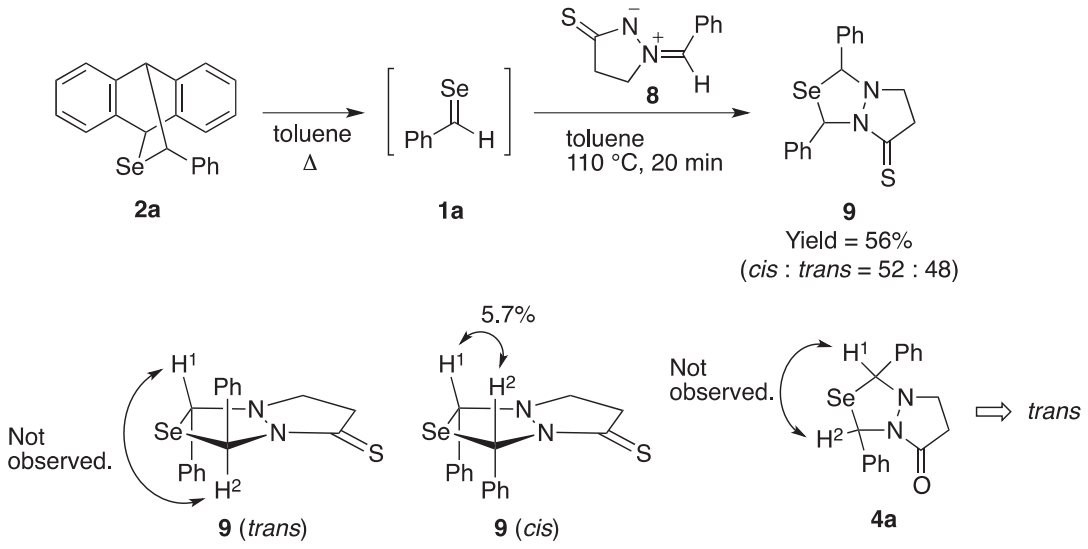
4 (E = Se)
7 (E = S)

Entry	Precursor of Chalcogenoaldehyde			Cyclic Azomethine Imine		Temp. (°C)	Time	Product	Yield[b)] (%)
		E	R		R'				
1	**2a**	Se	Ph	**3a**	Ph	110	3 h	**4a**	19
2	**2a**	Se	Ph	**3a**	Ph	110	1 h	**4a**	72
3	**2a**	Se	Ph	**3a**	Ph	110	30 min	**4a**	73
4	**2a**	Se	Ph	**3a**	Ph	110	10 min	**4a**	76
5	**2a**	Se	Ph	**3a**	Ph	150[c)]	10 min	**4a**	55
6	**2a**	Se	Ph	**3a**	Ph	90	8 h	**4a**	69
7	**2b**	Se	*p*-$MeOC_6H_4$	**3a**	Ph	110	10 min	**4b**	85
8	**2c**	Se	*p*-NCC_6H_4	**3a**	Ph	110	10 min	**4c**	94
9	**2d**	Se	*n*-Pr	**3a**	Ph	160[c)]	20 min	**4d**	69[d)]
10	**2a**	Se	Ph	**3b**	*p*-MeC_6H_4	110	10 min	**4e**	81
11	**2a**	Se	Ph	**3c**	*p*-$MeOC_6H_4$	110	10 min	**4f**	88
12	**2a**	Se	Ph	**3d**	*p*-$CF_3C_6H_4$	110	10 min	**4g**	65
13	**2a**	Se	Ph	**3e**	1-naphthyl	110	10 min	**4h**	62
14	**2a**	Se	Ph	**3f**	*t*-Bu	110	10 min	**4i**	73
15	**2c**	Se	*p*-NCC_6H_4	**3d**	*p*-$CF_3C_6H_4$	110	10 min	**4j**	95
16	**6a**	S	Ph	**3a**	Ph	110	10 min	**7a**	85
17	**6b**	S	*p*-$MeOC_6H_4$	**3a**	Ph	110	10 min	**7b**	76
18	**6c**	S	*p*-NCC_6H_4	**3a**	Ph	110	10 min	**7c**	96
19	**6d**	S	*n*-Pr	**3a**	Ph	160[c)]	20 min	**7d**	99[e)]

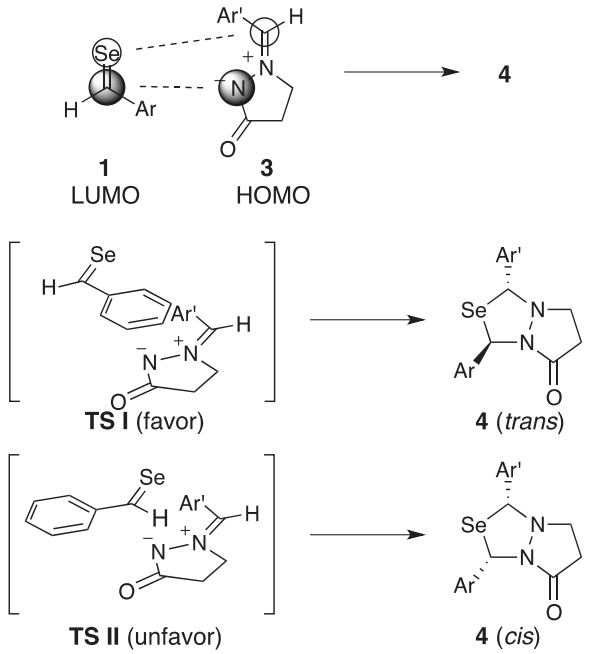
a) Conditions: precursor of chalcogenoaldehyde (**2** or **6**, 0.5 mmol), cyclic azomethine imine (**3**, 1.5 mmol), toluene (6 mL).
b) Isolated yield. c) In a sealed tube. d) Ratio of isomers = 91 : 9. e) Ratio of isomers = 92 : 8.

Cyclic azomethine imines used in this study, 2-arylmethylidene-5-oxopyrazolidin-2-ium-1-ides (**3**), are known to be stable compounds that can be easily prepared by reaction of pyrazolin-3-one with benzaldehyde derivatives as a stereoisomeric pure form (*Z* form).[27] A toluene solution containing Diels-Alder adduct of selenobenzaldehyde (**2a**) and (*Z*)-2-benzylidene-5-oxopyrazolidin-2-ium-1-ide (**3a**) was refluxed for 3 h under argon atmosphere (Table 1, entry 1). Purification by silica gel column chromatography gave 1,3-diphenyldihydro-1*H*-pyrazolo[1,2-*c*][1,3,4]selenadiazol-5(3*H*)-one (**4a**) in 19% isolated yield as a single stereoisomer, *trans* form (*vide infra*). Shortening of the reaction time resulted in increase of the yields (entries 2 and 3), and the best yield was obtained when the reaction was carried out at 110 °C for 10 min (entry 4).[33] Both elevated reaction temperature (150 °C) and lowered one (90 °C) did not improve the yield (entries 5 and 6). *p*-Methoxy- and *p*-cyano-substituted selenobenzaldehydes (**1b-c**) generated in situ also reacted with **3a** to give the corresponding heterocycles **4b-c** in high yields (entries 7 and 8). Selenobutanal (**1d**), an aliphatic selenoaldehyde, could also be used in the [3+2] cycloaddition when it was reacted with **3a** at 160 °C (for requirement of generation of aliphatic selenoaldehydes[17]), giving **4d** in 69% yield as a 91 : 9 diastereomeric mixture (entry 9). Cyclic azomethine imines **3b-f** having *p*-methylphenyl, *p*-methoxyphenyl, *p*-trifluoromethylphenyl, 1-naphthyl, and *tert*-butyl groups could also be used to give [3+2] cycloaddition products **4e-i** in 62-88% yields (entries 10-14). Combination of double electron-withdrawing aryl groups in **2** and **3** made the yield increase up to 95% (entry 15). Similarly, thiobenzaldehydes **5** generated by thermal reaction from analogous precursors **6a-d** reacted with **3a** to give the corresponding sulfur analogues **7a-d** in high yields (entries 16-19).

All products listed in Table 1 were obtained as a single stereoisomer with the exception of **4d** and **7d** which contained small amounts of another diastereomers. On the contrary, when thione derivative **8** was



Scheme 2. NOE Experiments Deducing Stereochemistry of Products

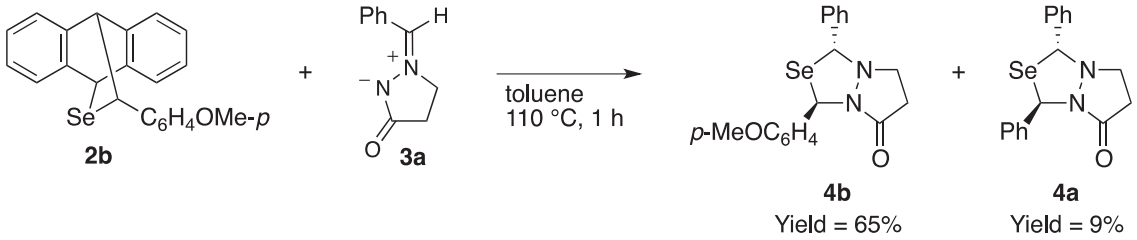


Scheme 3. Possible Explanation for Regio- and Stereochemistry of the [3+2] Cycloaddition

allowed to react with **2a**, the product **9** was produced in 52 : 48 diastereomer ratio (Scheme 2). NOE irradiation experiments indicated that 5.7% enhancement of integration of NMR signals between two benzylic hydrogens (H^1 and H^2) of **9** was observed only in one isomer and the enhancement was not observed from another isomer, so each benzylic hydrogens can be assigned to *cis* and *trans* isomers, respectively. Since NOE irradiation of **4a** under the same conditions did not show any enhancement, we determined the stereochemistry of **4a** as *trans* isomer. The *trans* configuration is also expected to other products **4b-j** and **7a-d** from similarity of their ^{1}H NMR spectra with that of **4a**.

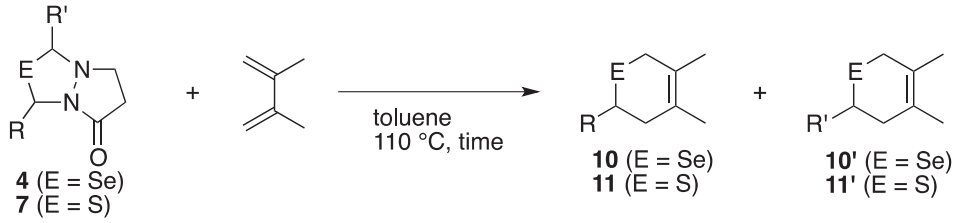
From these results, we propose a possible mechanism for the [3+2] cycloaddition as shown in Scheme 3. Excellent regioselectivity can be explained by interaction of LUMO of **1** and HOMO of **3**, whose orbital coefficients spread on selenocarbonyl carbon of **1** and nitrogen at 1-position of **3** larger than the selenium and benzylidene carbon, respectively.[28, 34-36] As for the excellent stereoselectivity giving *trans* isomers, we would like to propose effective orbital interaction between aryl group of **1** and π orbitals including carbonyl group of **3**. Hence, when the two addends approach each other, **TS I** where aryl group of **1** locates on *endo*-position toward **3** may be favored rather than **TS II** where the aryl group locates on *exo*-position. The large difference of the *cis* / *trans* ratio between the reactions using **3a** and **8** may be due to the weakened orbital interaction between **1** and **8**.

From the entries 1-4 in Table 1, the time profile suggests that thermal decomposition of the product **4** might be involved. Indeed, when reaction of **2b** with **3a** was carried out at 110 °C for 1 h, a diphenyl



Scheme 4. Reaction of **2b** with **3a** Giving Two [3+2] Cycloaddition Products

Table 2. Cycloreversion of [3+2] Cycloadducts and Trapping of Seleno- and Thioaldehydes with 2,3-Dimethyl-1,3-butadiene[a)]

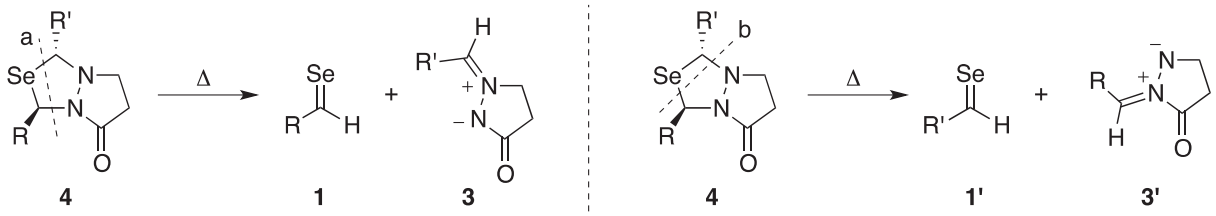


Entry	[3+2] Cycloadduct				Time (h)	Yield(s)[b)] (%)	
		E	R	R'		**10** or **11**	**10'** or **11'**
1	**4b**	Se	*p*-$MeOC_6H_4$	Ph	3	82 (**10a**)	3 (**10b**)
2	**4c**	Se	*p*-NCC_6H_4	Ph	1	95 (**10c**)	2 (**10b**)
3	**4e**	Se	Ph	*p*-MeC_6H_4	1	93 (**10b**)	–[c)]
4	**4g**	Se	Ph	*p*-$CF_3C_6H_4$	3	95 (**10b**)	–[c)]
5	**7b**	S	*p*-$MeOC_6H_4$	Ph	2.5	82 (**11a**)	4 (**11b**)
6	**7c**	S	*p*-NCC_6H_4	Ph	1.5	87 (**11c**)	3 (**11b**)

a) Conditions: [3+2] cycloadduct (**4** or **7**, 0.4 mmol), 2,3-dimethyl-1,3-butadiene (2.0 mmol), toluene (6 mL), 110 °C.
b) Isolated yield. c) Not detected.

derivative **4a** was obtained in a minor extent with the formation of main product **4b**, in spite of that unsubstituted selenobenzaldehyde should not be formed from thermolysis of **2b** (Scheme 4). These results prompted us to investigate thermal cycloreversion of **4** at 110 °C to regenerate selenoaldehydes **1** (Table 2). When **4b** was allowed to treat with excess amount of 2,3-dimethyl-1,3-butadiene at 110 °C for 3 h, Diels-Alder adducts **10a** and **10b**, which indicate generation of *p*-methoxyselenobenzaldehyde and unsubstituted selenobenzaldehyde, were obtained in 82% and 3% isolated yields, respectively (entry 1). Reaction of some other derivatives **4c**, **4e**, and **4g**, or thio derivatives **7b-c**, also resulted in major production of **10** or **11** and minor production of **10'** or **11'** (entries 2-6).

From these results, the regioselective cycloreversion of **4** and **7** giving seleno- and thioaldehydes **1** and **5**, respectively, is rationalized as depicted in Scheme 5. Thermal bond cleavage at position a, i.e. the retro reaction of the cycloaddition, gives the starting materials **1** and **3**, whereas bond cleavage at position b produces **1'** and 1,3-dipole species **3'**. As expected from structures **3** and **3'**, **3'** seems to be thermodynamically more unstable than **3** because **3'** has cationic nitrogen atom on α-position of



Scheme 5. Regioselective Bond Cleavage in Thermal Cycloreversion of [3+2] Cycloadducts

electron-withdrawing carbonyl group. This assumption is not inconsistent with the results that generation of **1** is a major pathway and that of **1'** is a minor pathway. Existence of route b in Scheme 5 is also supported from the experimental results in the reaction of **2b** with **3a** shown in Scheme 4. As a reason for decreasing the yield of **4** by longer reaction time of [3+2] cycloaddition at 110 °C (entries 1-4 in Table 1), the [3+2] cycloaddition proceeds in an equilibrium with regioselective cycloreversion, so the reproduced selenoaldehyde gradually decomposes during the reaction.

In conclusion, we have developed a novel and stereoselective [3+2] cycloaddition reaction between seleno- and thioaldehydes generated in situ with cyclic azomethine imines to give novel selenium-containing bicyclic heterocycles in high yields. *Trans* configuration of 1,3-diaryl groups of products was determined by NOE experiments of thione derivatives. Regio- and setereoselectivity can be explained by orbital coefficients of two addends and orbital overlapping at transition states, respectively. Cycloreversion giving selenoaldehydes and cyclic azomethine imines competes with the [3+2] cycloaddition, and it occurs at two types of bond cleavage patterns, in which retro-type reaction is a major pathway.

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33. *Typical procedure for [3+2] cycloaddition:* To an argon-purged, two-necked, 20 mL round-bottom flask equipped with a reflux condenser and a magnetic stirrer, toluene (6 mL), compound **2a** (174 mg, 0.5 mmol), and cyclic azomethine imine (**3a**, 261 mg, 1.5 mmol) were placed. The solution was heated to 110 °C by an oil bath and stirred for 10 min. After cooling to 0 °C by an ice bath, saturated NH_4Cl aqueous solution was added. The organic layer was extracted, dried over $MgSO_4$, and evaporated. Column chromatography on silica gel (eluent; hexane : ethyl acetate = 2 : 1) gave pure product, *trans*-1,3-diphenyldihydro-1*H*-pyrazolo[1,2-*c*][1,3,4]selenadiazol-5(3*H*)-one (**4a**, 130 mg, 76% yield). *Spectral data for **4a**:* ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.61 – 7.23 (m, 10H), 6.74 (s, 1H), 5.52 (s, 1H), 3.60 (ddd, *J* = 12.7, 10.7, 8.8 Hz, 1H), 3.16 – 3.07 (m, 1H), 2.91 (ddd, *J* = 9.0, 10.7, 17.6 Hz, 1H), 2.49 (ddd, *J* = 17.6, 8.8, 2.0 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$): δ 173.1, 141.7, 135.5, 128.9, 128.7, 128.5, 127.7, 126.5, 73.5, 53.2, 44.7, 28.8; ^{77}Se NMR (76 MHz, $CDCl_3$): δ 692.66; MS (EI), m/e (relative intensity): 344 (M^+, 98.0), 260 (12.6), 175 (100), 170 (98.3), 105 (54.5), 84 (33.5); HRMS (EI) Calcd for $C_{17}H_{16}N_2OSe$: 344.0428; Found: 344.0430.
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